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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,264	12/19/2001	Binoy Appukuttan	D6124	5702

7590 11/07/2003

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,264	APPUKUTTAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 December 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

► *Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm).* The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306.**

Election/Restrictions

Applicant's election with traverse of Group VI claims 5-10 *(elected disease: age-related macular degeneration; elected therapeutic gene: a fusion protein of Mig and IP10)* in Paper No. 10/01/03 is acknowledged. The traversal is on the ground(s) that regardless of etiology age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity and glaucoma are the diseases that exhibit neovascularization leading to blindness. The applicant argues that the search required does not impose an undue burden on the office. Therefore Groups VII-X should be rejoined with Group VI. However, this is found NOT persuasive because each of the above mentioned diseases have distinct etiology. For example proliferative diabetic retinopathy is the result of high levels of blood sugar and/or insulin (a growth factor) in blood, whereas glaucoma is associated with elevated IOP induced by trabecular meshwork. Therefore there exists a serious search burden to examine all these disease as one single invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10/01/03.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless - -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 5-8 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Murata et al (Ophthalmology 10(7):1364-73, 2000).

Instant claims are drawn to a method of inhibiting intraocular neovascularization in an individual having an ocular disease by administering a lentiviral vector comprising a therapeutic gene that inhibits intraocular neovascularization.

The cited art teaches a method for gene therapy for the treatment of choroidal neovascularization (CNV) in age-related macular degeneration. The cited art teaches making CNV lesions in cynomolgus monkey by laser photocoagulation followed by injection of a retroviral vector encoding TIMP-2 into the subretinal space (intracocular) overlying CNV lesions (page 1367, col.1 para.4). The cited art further teaches that delivery of TIMP-2 vector to CNV lesions in monkey eye supports the feasibility for the treatment of choroidal neovascularization. (page 1369, col.2 para. 3, page 1370, fig-7). The cited art concluded that when TIMP-2 encoding retrovirus was injected in the vicinity of a developing CNV lesion in vivo in a monkey model a clinically observable and apparently antiangiogenic effect was found (page 1371, col.2 para.2). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting intraocular neovascularization in cornea by administering a lentiviral vector encoding Mig/IP10 fusion protein, does not reasonably provide enablement for a method of inhibiting neovascularizatin in any other intraocular tissues (iris, lens, retina, choroidal vasculature, sclera or photoreceptor cells) by administering a lentiviral vector encoding any therapeutic gene into any target site in an individual having any intraocular disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of Invention:

Invention relates to a method of inhibiting intraocular neovascularization in age-related macular degeneration by administering a lentiviral vector encoding a fusion protein of Mig/IP10 or a gene that regulates apoptosis.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses a method of inhibiting neovascularization (in age-related macular degeneration) by administering a lentiviral vector comprising therapeutic gene that regulate angiogenesis or apoptosis, wherein the vector is administered any intracoular tissue (iris, lens, sclera, retina, photoreceptor cells, optic nerve cells

etc). At best the specification teaches in-vitro transduction of human retinal pigment epithelial cells (RPE), human umbilical vein endothelial cells (HUVEC), Choroidal fibroblasts (CF), human retinoblastoma (retinal-derived) cells (Weri- Rb-1 and Y79) and human cornel cells using a MLV vector encoding a marker gene (Spec. pages 9-12). The specification further disclosed a rabbit model for alkali-induced neovascularization in **corneal tissue** (spec. page 57). The specification disclosed an inhibitory effect on neovascularization in animals treated with a Mig/1P10 vector (Spec. page 60 table-1, Fig-34). However, the specification fails to disclose that intraocular administration of a lentiviral vector encoding Mig/IP10 fusion protein or any apoptotic protein (as claimed) resulted in the inhibition of neovascularization in degenerated macular tissue. Furthermore the specification fails to provide any guidance what are the target intraocular tissues transduction of which would inhibit neovascularization in the age related macular degeneration.

State of Art and Predictability

Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Friedmann, Science 287(5461):2163-5, 2000, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a

greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para 3). Although increasing numbers of genes responsible for retinal degenerative diseases have recently been identified, the underlying mechanism of retinal degeneration is not well understood and there are no adequate therapies for these diseases at present (Miyoshi et al, PNAS. 94-10319-10323, 1997; see col.1 para.1). Furthermore choroidal vasculature is the source of blood nourishment of intraocular structures but choroidal-neovascularization (CNV) leads to age related macular degeneration (AMD) in people after age 60 (Borras, Exp. Eye Res. 76 :643-652, 2003, page 646, sec.5). Besides customary laser photocoagulation procedure there is no known anti-angiogneic treatment for patients with ocular neovascularization. In instant case the invention as claimed requires the inhibition of intraocular neovascularization by transducing any type of ocular tissue (lens, retina, iris, sclera, photoreceptor cells) by administering a lentiviral vector encoding a Mig/IP10-fusion protein or a protein that regulate apoptois. The specification fails to disclose the role Mig and IP10 chemokines or any apoptotic protein in the development of age related macular degeneration. The state of the art at the time of filing was such that Mig and IP10 are potent chemo-attractants that recruits NK1 cells and Th1 lymphocytes leading to an inflammatory immune response (Gasperini et al, The Journal of Immunology, 162: 4928-4937, 1999, see abstract). The specification as filed fails to disclose that intraocular injection of a lentiviral vector encoding Mig/Ip10 fusion protein would transduce any intraocular tissue (lens, retina, iris, sclera), since vitreous humor is gelatinous substance that would hinder the transduction of target cells. Similarly the specification fails to provide any evidence that administration of letiviral vector encoding any pro-apoptotic protein would only selectively inhibit choroidal

neovascularization while sparing the retinal epithelium, photoreceptor cells and neurons of optic nerve. On the other hand the specification fails to disclose that administration of a retroviral vector encoding Bcl-2 (survival gene) would inhibits intracoular neovascularization. Regarding Bcl-2, the state of the art at the time of filing was such that over expression of Bcl-2 by retroviral transduction not only resulted in prolonged survival of human vascular endothelial cells (EC) but also allowed incorporation of human EC in mouse capillaries in vivo (see Schechner et al, PNAS 97(16):9191-9196, 2000). Therefore the specification as filed is not enabled for the scope of invention as claimed.

The courts have clearly stated that: a specification needs not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

Furthermore gene based therapies for choroidal-neovascularization (CNV) in age-related macular degeneration (AMD) are not routine in the art and without sufficient guidance to a

specific therapeutic effects of Mig/IP10 fusion protein and/or a protein that regulates apoptosis the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER